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Korang SK, Safi S, Feinberg J, Gluud C, Perner A, Jakobsen JC.
Higher versus lower blood pressure targets in adults with shock.
Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD013470.
DOI: 10.1002/14651858.CD013470.

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TABLE OF CONTENTS

[Intervention Protocol]

Higher versus lower blood pressure targets in adults with shock

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Editorial group: Cochrane Emergency and Critical Care Group
Publication status and date: New, published in Issue 11, 2019.

Citation: Korang SK, Safi S, Feinberg J, Gluud C, Perner A, Jakobsen JC. Higher versus lower blood pressure targets in adults with shock. *Cochrane Database of Systematic Reviews* 2019, Issue 11. Art. No.: CD013470. DOI: 10.1002/14651858.CD013470.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the beneficial and harmful effects of higher versus lower blood pressure targets in patients with any type of shock.

BACKGROUND

Description of the condition

Definition and pathophysiology

Shock is commonly defined as life-threatening acute circulatory failure that leads to inadequate tissue perfusion and thereby to inadequate oxygen utilization by the cells (Cecconi 2014; Vincent 2013). Low blood pressure is not a necessity for shock, as compensatory vasoconstriction may preserve a normal blood pressure (van Genderen 2013; Wo 1993). Inadequate tissue perfusion is apparent through the clinical sign known as the three 'windows' of the body. These windows are the kidneys (urine output of less than 0.5 mL/kg body weight/hour), neurological status (altered mental state, which typically includes obtundation, disorientation, and confusion), and to a certain extent skin (cold and clammy skin, with vasoconstriction and cyanosis) as cutaneous alterations may be absent in vasoplegic states (Vincent 2013).

Shock may be divided into four different subgroups according to its underlying pathophysiological differences (Richards 2014; Vincent 2013). They include vasodilatory shock (e.g. septic shock, anaphylactic shock, neurogenic shock, toxin-related shock, and endocrine shock), hypovolemic shock (e.g. haemorrhage and different causes of dehydration), cardiogenic shock (e.g. pulmonary hypertension, free wall rupture, ventricular septal rupture, chordae tendineae or papillary muscle rupture, valvular disease, cardiac tamponade, or a pulmonary embolism causing right ventricular heart failure), and obstructive shock (e.g. pulmonary embolism, pneumothorax, or pericardial tamponade) (Amado 2016; Anderson 2013; Beesley 2017; Brown 2007; Dave 2018; Gaieski 2016; Goldberg 2001; Hands 1989; Kobayashi 2012; McMahon 2009; Moranville 2011; Nduka 2009; Rhodes 2017; Shah 2014; Singer 2016; Szopinski 2011; Vincent 2013).

In addition to the aforementioned pathophysiological classification of different types of shock, some patients might have a combination of more than one form of shock (multifactorial shock) (Richards 2014; Vincent 2013).

A large Danish cohort study showed that 0.4% of patients in the hospital emergency department had shock on arrival (Holler 2016). A European multicentre cohort study suggests that up to one-third of patients admitted to the intensive care unit (ICU) had shock during their admission (Sakr 2006). The most common form of shock among patients admitted to the ICU is septic shock, which is seen in 6% to 15% of patients admitted to the ICU (Antonelli 2007; Quenot 2013). Septic shock is followed by cardiogenic and hypovolaemic shock. Obstructive shock and anaphylactic shock are rare (De Backer 2010; Vincent 2013). In a European trial consisting of 1600 patients with undifferentiated shock, septic shock was found in 62%, cardiogenic shock in 16%, hypovolaemic shock in 16%, other types of vasodilatory shock in 4% (e.g. neurogenic shock, anaphylactic shock), and obstructive shock in 2% (De Backer 2010). When assessing shock, in general, mortality is approximately 38%, but rates vary depending on the type of shock (Sakr 2006). A prospective observational study found that septic shock is associated with mortality rates ranging from 46% to 61% (Alberti 2005; Esteban 2007; Pavon 2013), and cardiogenic shock is considered to have a similar mortality rate (59%) (Awad 2012). In contrast, mortality is estimated to be under 1% in people with anaphylactic shock, which is less common (Antonelli 2007; Jeppesen 2016; Ma 2014).

Description of the intervention

Treatment of shock usually involves treating the underlying cause, as well as promoting a haemodynamic stabilization through the use of fluid resuscitation and vasoactive agents (Cecconi 2014).

Interventions for raising the blood pressure

Early haemodynamic stabilization is a high priority in the management of patients with shock (Levy 2018; Møller 2016; Rhodes 2017; Rossaint 2016; Vincent 2013). The initial support often includes intravascular fluid resuscitation in combination with the administration of a vasopressor (Levy 2018; Rhodes 2017; Rossaint 2016; Vincent 2013). Other agents used for shock resuscitation include corticosteroids, blood products, colloids (e.g. albumin, dextran, gelatin), and inotropic agents (Rhodes 2017; Roth 2015; Venkatesh 2018).

Current guidelines for septic shock and critically ill adults with hypotension recommend targeting a mean arterial pressure (MAP) of less than 65 mmHg (Greenwood 2017; Levy 2018; Rhodes 2017; Rochwerg 2017). However, patients with chronic hypertension and haemorrhagic shock with brain injury may benefit from having a higher blood pressure target (Post 2018; Rossaint 2016; Strandgaard 1973). A randomized clinical trial also showed a reduced need for renal replacement therapy and lower plasma creatinine when randomizing septic patients with chronic hypertension to a higher blood pressure target (Asfar 2014). Consistent with this, some guidelines suggest targeting a higher MAP of around 80 to 85 mmHg in patients with known chronic hypertension (Kato 2015). On the other hand, patients with haemorrhagic shock without brain injury might benefit from a lower blood pressure target (Rossaint 2016). Elderly patients (75 years of age and older) might also benefit from a lower blood pressure target (Lamontagne 2016).

Intravenous fluids

Initially, intravenous fluids are typically used regardless of the type of shock (Levy 2018; Rhodes 2017; Rossaint 2016; Vincent 2013). Isotonic fluids (similar tonicity to body fluids around 300 mmol/L), such as 0.9% (w/v) sodium chloride or hypotonic balanced/physiological solutions, are the preferred solutions for resuscitation as they expand the intravascular volume without causing cellular fluid shifts (Krausz 2006; Myburgh 2013; Rhodes 2017; Siegel 1970). Another widely used type of isotonic fluid is colloids. A recent Cochrane Review did not find colloids of any kind (starches, dextrans, albumin, fresh frozen plasma, or gelatins) to be superior to crystalloids regarding mortality (Lewis 2018). As colloids are more expensive, recommendations advise using crystalloids as the first-line therapy for fluid resuscitation (Rhodes 2017). The results of the Cochrane Review by Lewis 2018 are inconsistent with an earlier Cochrane Review, which showed that the most commonly used type of colloid 'hydroxyethyl starch' increased mortality for critically ill patients compared with saline (Perel 2013).

Vasopressors

Clinical guidelines recommend norepinephrine as the first-line vasopressor in patients with shock (Belletti 2017; Levy 2018; Møller 2016; Rhodes 2017). Norepinephrine is the preferred vasopressor, followed by dopamine and epinephrine in critically ill patients (Cecconi 2015; Sakr 2006). However, no significant difference has been observed between the different vasopressors with regard to mortality, except when comparing norepinephrine with dopamine for

patients with cardiogenic shock (where norepinephrine was superior) (De Backer 2010; Gamper 2016).

Glucocorticosteroids

Hydrocortisone is recommended for treatment of septic shock if adequate fluid resuscitation and vasopressor therapy are unable to restore haemodynamic stability (Rhodes 2017). Hydrocortisone does not seem to affect mortality, but rather shortens the time until shock reversal (Venkatesh 2018).

How the intervention might work

The purpose of having a blood pressure target is to create a surrogate for the restoration of adequate tissue perfusion that is absent in people with shock. Therefore, the goal of the haemodynamic interventions is to increase the blood pressure to the point at which sufficient tissue perfusion and cellular metabolism are achieved (Arnemann 2016; Rivers 2001; Vincent 2013).

A higher blood pressure target may, therefore, ensure better perfusion to vital organs. Higher blood pressure targets have been associated with improved mortality (MAP above 60 to 65 mmHg) and less renal dysfunction (MAP above 75 mmHg) in non-randomized studies of septic shock patients (Badin 2011; Dünser 2009; Kato 2015; Varpula 2005).

The benefits of having a lower blood pressure target might be that the use of interventions with potential harmful adverse effects are avoided. Also patients, such as trauma patients with ongoing bleeding (excluding brain injury), might benefit from a lower blood pressure target because the risk of rebleeding might be reduced (Rossaint 2016).

Fluid administration and other volume expanders are thought to improve the stroke volume of the heart by optimizing the pre-load and thereby increasing the cardiac output (Frank-Starling mechanism). Theoretically, this might in turn increase and restore the effective blood volume, which might ultimately ensure better tissue perfusion (Frazee 2016; Marik 2016; Starling 1927).

Aggressive crystalloid resuscitation might cause oedema which may lead to serious adverse events, such as abdominal compartment syndrome and pulmonary oedema (Carlotti 2009; Cotton 2006). Fluid resuscitation also causes a dilution of clotting factors and induces platelet dysfunction, which in turn might result in a poorer response to bleeding (Balogh 2003; Cotton 2006). It has also been shown to cause cardiovascular dysfunction, ileus, and renal failure (Balogh 2003; Cotton 2006; Hjortrup 2016). In addition, excessive administration of saline may lead to hyperchloraemic metabolic acidosis (Myburgh 2013).

Vasopressors are a group of drugs that induce vasocontraction in the blood vessels, thereby elevating the arterial pressure (Golan 2011; Katzung 2007). Vasopressors aim to restore organ perfusion pressure during acute resuscitation in patients with shock (Amado 2016; Moranville 2011; Rhodes 2017).

Interventions for raising the blood pressure might normalize macrocirculation values (heart rate, heart rhythm, cardiac filling, cardiac output, arterial oxygen saturation, etc.), while a defect at the microcirculation level could still exist (Dubin 2009; Weil 2009). The cardiac dysfunction seen in septic shock might be closely linked to pathological microcirculatory alterations, and increasing blood pressure might not be beneficial (De Backer 2010).

Several possible harmful effects of vasopressors have been proposed by observational studies, such as arrhythmias, cardiac cell injury, ischaemic skin lesions, visceral ischaemia, and worsening regional perfusion (Bulkley 1986; D'Aragon 2015; Dünser 2003; McIntyre 2018; Pawlik 1975; Schmittinger 2012). Some of these adverse effects (e.g. atrial fibrillation) can be avoided by combining catecholamines with non-adrenergic vasopressors such as vasopressin (Belletti 2015; McIntyre 2018).

Why it is important to do this review

Observational studies have shown that a MAP below 65 mmHg is associated with a higher mortality in patients with septic shock (Dünser 2009; Kato 2015; Varpula 2005). However, while several trials have shown no indication of a beneficial effect of targeting a MAP of 65 mmHg or more, there might be an increase in serious adverse events (such as arrhythmias) if a higher MAP (80 to 85 mmHg) target is chosen (Asfar 2014; Beloncle 2016; Bourgoin 2005; LeDoux 2000; Thooft 2011).

Observational evidence shows that vasopressors might cause direct organ damage and seem to be associated with harmful effects on the metabolic, immune, and coagulation systems (Andreis 2016; Hessler 2016). In addition, observational studies suggest that the risk of adverse events due to vasopressor use ranges from 10% to 12% (Annane 2007; De Backer 2010; Russell 2008).

Two recent meta-analyses assessing blood pressure targets for patients with septic shock and vasodilatory shock did not find any specific blood pressure target to be superior (D'Aragon 2015; Lamontagne 2018). To our knowledge, no systematic review has assessed the beneficial and harmful effects of higher versus lower blood pressure target in patients with all types of shock.

OBJECTIVES

To assess the beneficial and harmful effects of higher versus lower blood pressure targets in patients with any type of shock.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized clinical trials. We will exclude quasi-randomized trials. We will include cross-over trials, but will only extract data from before the cross-over occurs. We will include trials regardless of publication type, publication status, publication period, and language of publication.

Types of participants

We will include any adults (as defined by the trial authors) with a diagnosis of shock (as defined by trial authors). We will exclude patients with ruptured abdominal aortic aneurysm, to avoid overlap with an existing Cochrane Review (Moreno 2018).

Types of interventions

The experimental intervention will be any intervention or combination of interventions aiming at a higher blood pressure target (as defined by trial authors). The control intervention will be any in-

tervention or combination of interventions aiming at a lower blood pressure target (as defined by trial authors). To ensure that the targets in the compared groups differ meaningfully, we will only include trials that report at least two different blood pressure targets. We will include targets reported as diastolic, systolic, and mean arterial blood pressure. We will accept any co-intervention but only if this co-intervention is planned to be delivered similarly in both the experimental and the control group.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Proportion of participants with one or more serious adverse event. We will define a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, jeopardized the participant, was persistent, or led to significant disability, hospitalization, or prolonged hospitalization (ICH-GCP 1997). As we expect the reporting of serious adverse events to be very heterogeneous and not strictly reported according to the ICH-GCP recommendations in many trials, we will include the event as a serious adverse event if the trial authors either:
   a. use the term 'serious adverse event' but not refer to ICH-GCP, or
   b. report the proportion of participants with an event that we consider fulfils the ICH-GCP definition (e.g. myocardial infarction or hospitalization).

If several of such events are reported then we will choose the highest proportion reported in each trial.

Secondary outcomes

1. Health-related quality of life (any valid continuous scale used by the trial authors (e.g. SF 36)).
2. Proportion of participants with organ failure defined as either an acute change in total Sequential Organ Failure Assessment (SOFA) score 2 points or more (Singer 2016).
3. Length of ICU stay (in days).

We will assess all outcomes at two time points:

1. Outcomes assessed at the time point closest to one month (this is the time point of primary interest).
2. Outcomes assessed at maximal follow-up.

Search methods for identification of studies

Electronic searches

We will search for studies as described in Chapter 6 of the *Cochrane Handbook of Systematic reviews of Interventions* (Lefebvre 2011).

There will be no restrictions imposed on language, publication year, or publication status.

We will search the following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (latest Issue)
2. MEDLINE (Ovid SP, 1946 to date)
3. EMBASE (Ovid SP, 1974 to date)
4. Web of Science (1945 to date)
5. Other relevant databases such as CINAHL, PsycInfo, Biosis, Scopus, and LILACS.

We developed a draft MEDLINE search strategy (Appendix 1), which we will modify appropriately for the other databases. If we identify any papers in a language not known by the review author team, we will seek help outside of the review author group. We will acknowledge any assistance received in the 'Acknowledgements' section of the published review.

Searching other resources

We will check the bibliographic references and citations of relevant studies and reviews for further references to trials. We will also search ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) for unpublished and ongoing studies, Open Grey (http://opengrey.eu/) for grey literature, and Google Scholar for additional trials. When necessary we will contact trial authors for additional information.

Data collection and analysis

We will perform the analyses using Review Manager 5 (Review Manager 2014), Stata 15 (Stata 2014), and Trial Sequential Analysis (TSA) version 0.9.5.10 beta software (CTU 2011; Thorlund 2011).

Selection of studies

Two review authors (SKK and SS) will independently screen titles and abstracts according to the pre-specified inclusion criteria. We will retrieve all relevant full-text study reports/publications. Two review authors (SKK and SS) will independently screen the full-text reports and identify trials for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (JCJ). We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 1998), and 'Characteristics of excluded studies' table.

Data extraction and management

We will use data collection forms for trial characteristics and outcome data. These forms will be piloted on at least one trial selected for inclusion in the review. Two review authors (SKK and SS) will extract trial characteristics from the included trials. We will extract the following study characteristics.

1. Methods: trial design, total duration of the trial, risk of bias items, number of trial centres and location, trial setting, withdrawals, and date of the trial.
2. Participants: number of participants in each intervention group, mean age, age range, gender, type of shock, mean arterial blood pressure (during trial), prior history of chronic hypertension or traumatic brain injury, diagnostic criteria, withdrawals, inclusion criteria, and exclusion criteria.
3. Interventions: intervention and comparison. Co-interventions. Cumulative amount of interventions (e.g. fluid or vasoactive drugs) used during the trial.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: trial funding, and notable conflicts of interest of trial authors.

Two review authors (SKK and SS) will independently extract outcome data from included trials. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (JCJ). One review author (SKK) will transfer data into the Review Manager 5 file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SS) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

We will follow use the instructions in the *Cochrane Handbook for Systematic Reviews of Interventions* to guide our evaluation of the trial methodology and hence the risk of bias of the included trials (Higgins 2011). Two review authors (SKK and SS) will independently assess the included trials. We will evaluate the methodology used for generation of allocation sequence, allocation concealment, blinding of participants and treatment providers, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, for-profit bias, and other bias sources. Evaluation of these components will enable classification of randomized trials with an overall judgement of either low or high risk of bias. Trials at high risk of bias tend to be associated with more positive intervention effects and fewer negative effects (Gluud 2006; Kjaergard 2001; Lundh 2017; Moher 1998; Wood 2008; Savović 2012; Savovic 2017). We will classify the trials according to the components found in Appendix 2.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence intervals (CI) and TSA-adjusted CIs (Thorlund 2011), for dichotomous outcomes.

Continuous outcomes

We will calculate the mean differences (MDs) and the standardized mean differences (SMD) with 95% CI and TSA-adjusted CIs (Thorlund 2011), for continuous outcomes. We will use the SMD when the trials all assess the same outcome but measure it in a variety of ways (e.g. different scales) (Higgins 2011b).

Unit of analysis issues

If we find any cross-over trials, we will only include data from the first treatment period (before cross-over) (Elbourne 2002).

Where multiple trial arms are reported in a single trial, we will include only the relevant arms (that meet our inclusion criteria). If the trial has more than one relevant arm we will combine the treatment groups to make a single pair-wise comparison.

Dealing with missing data

We will contact trial investigators and trial sponsors in order to verify key trial characteristics and obtain missing outcome data where possible (e.g. when a study is identified as an abstract only).

We will perform an intention-to-treat analysis whenever possible. Otherwise, we will use the data that are available to us (e.g. a trial may have reported only per-protocol analysis results) (Higgins 2011b). As 'per-protocol' analyses may be biased, we plan to conduct two extreme case sensitivity analyses for our primary outcomes (see Sensitivity analysis; Hollis 1999).

Assessment of heterogeneity

First, we will inspect trial characteristics for signs of unexpected clinical heterogeneity.

Second, we will assess for signs of statistical heterogeneity through subgroup analyses. In addition, we will assess clinical and methodological heterogeneity by considering the methodology, design, and the results of the included trials.

Third, we will visually inspect forest plots for signs of statistical heterogeneity, i.e. if the point estimate and CI of each trial result seem to differ between the included trials e.g. if one or two trials seem to show different effects that the remaining trials (Nielsen 2019).

Fourth, we will assess the presence of statistical heterogeneity by measuring the level of heterogeneity using the I^2 statistic (Higgins 2002; Higgins 2003), following the recommendations for thresholds stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may represent considerable heterogeneity.

Ultimately, we will consider not conducting the overall meta-analysis if the subgroup analysis shows different effects and the overall meta-analysis shows substantial heterogeneity (Higgins 2011b).

Assessment of reporting biases

We will use a funnel plot to assess reporting bias if 10 or more trials are included. We will visually inspect funnel plots to assess the risk of bias. For dichotomous outcomes, we will test asymmetry with the Harbord test (Harbord 2006). For continuous outcomes, we will use the regression asymmetry test (Egger 1997), and the adjusted rank correlation (Begg 1994).

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will use the statistical software Review Manager 5 (Review Manager 2014), provided by Cochrane, to analyse data.

We will assess our intervention effects with both random-effects meta-analyses (DerSimonian 1986), and fixed-effect meta-analyses (DeMets 1987). We will use the more conservative point estimate (closest to zero effect) of the two (Jakobsen 2014). If the two estimates are similar, we will use the estimate with the widest CI. As two primary outcomes are specified, we will consider a P value of 0.033 or less as the threshold for statistical significance (Jakobsen 2014). As a secondary analysis, we will use the eight-step procedure to assess if the thresholds for significance are crossed (Jakobsen

2014). Where data are only available from one trial, we will use Fisher's exact test (Fisher 1922), for dichotomous data and Student's t-test for continuous data (Student 1908).

We plan to use meta-regression to assess whether different blood pressure targets seem to influence the results of the primary outcomes.

In addition to the primary meta-analysis, we plan to conduct TSA as a secondary analysis (see Appendix 3).

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses.

1. Comparison of the aggregated effects of interventions between trials at low and high risk of bias.
2. Comparison of the aggregated effects of interventions between trials with vasodilatory versus any non-vasodilatory type of shock.
3. Comparison of the aggregated effects of interventions between trials with different types of shock (e.g. cardiogenic shock, obstructive shock, hypovolaemic shock, anaphylactic shock, septic shock, toxin-related shock, endocrine shock, and neurogenic shock).
4. Comparison of the aggregated effects of interventions between trials with known chronic hypertension versus without chronic hypertension.
5. Comparison of the aggregated effects of interventions between trials with traumatic brain injury versus without traumatic brain injury.
6. Comparison of the aggregated effects of interventions between trials with haemorrhagic shock injury versus without haemorrhagic shock injury
7. Comparison of the aggregated effects of interventions between trials where the same interventions were used in both groups to reach their targets and trials where the interventions differed amongst the groups.
8. Comparison of the aggregated effects of interventions between trials with participants less than 75 years of age versus trials with participants 75 years of age and older.

Sensitivity analysis

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses on the primary outcomes.

1. 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group have survived and have not had a serious adverse event; and all those participants with missing outcomes in the control group have not survived and have had a serious adverse event.
2. 'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group have not survived and have had a serious adverse event and that all those participants lost to follow-up in the control group had survived and have not had a serious adverse event.

When analysing continuous outcomes, a 'beneficial outcome' will be the group mean plus two standard deviations (SDs) (we will also use one SD in a separate analysis) of the group mean, and a 'harmful outcome' will be the group mean minus two SDs (we will also use one SD in a separate analysis) of the group mean (Jakobsen 2014). We will present the results of both scenarios in our review.

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis. Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials. We will present the results of this scenario in our review.

We will also conduct sensitivity analysis excluding trials where the lower blood pressure target group has a higher target than the higher blood pressure target groups in most of the included trials, and we will exclude trials where the higher blood pressure target group has a lower target than the lower blood pressure target groups in most of the included trials.

Other post-hoc sensitivity analyses might be warranted if we identify unexpected clinical or statistical heterogeneity during the analysis of the review results (Jakobsen 2014). We will disclose any new sensitivity analyses not reported in this protocol in the 'Differences between protocol and review' section of the systematic review.

Summary of findings and GRADE

We will use GRADE to assess the quality of the body of evidence associated with each of the primary outcomes (all-cause mortality and serious adverse events), and each of the secondary outcomes (quality of life, organ failure, and length of ICU stay) in our review. We will construct 'Summary of findings' tables using the GRADEpro GDT (GRADEpro GDT) (Guyatt 2008). We will use methods and recommendations described in Chapter 8 (Section 8.5) (Higgins 2011a), and Chapter 12 (Schünemann 2011), of the *Cochrane Handbook for Systematic Reviews of Interventions*. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. We will assess the GRADE levels of evidence as either high, moderate, low, or very low and will downgrade the evidence by one or two levels depending on the following quality measures: within study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias (Guyatt 2008). Two review authors (SKK and SS) will assess the quality of evidence independently and decide on downgrading. If no agreement can be reached, a third review author (JCJ) will resolve the discussion. We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

ACKNOWLEDGEMENTS

We thank Jasmin Arrich (Content Editor); Atul Malhotra, Neill KJ Adhikari, Alexandra Rose, and Jean-Louis Vincent (Peer Reviewers); Janne Vendt (Cochrane Information Specialist); Teo Quay and Jane Cracknell (Managing Editors); and Harald Herkner (Co-ordinating Editor) for their help and editorial advice during the preparation of this protocol.

The following Editors screened an earlier version of the draft protocol: Jane Cracknell, Harald Herkner, Ann Møller, Nathan Pace, Andy Smith, Marialena Trivella, and Janne Vendt.

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APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Fluid Therapy/

2 exp Isotonic Solutions/

3 exp Vasoconstrictor Agents/

4 exp dobutamine/

5 exp dopamine/

6 exp Colloids/

7 exp epinephrine/

8 exp norepinephrine/

9 exp Albumins/

10 exp Dextrans/

11 exp Glucocorticoids/

12 exp Hydrocortisone/

13 Gelatin/

14 ((intraven* or isotonic or hypotonic) and (fluid* or solution*)).mp.

15 (crystalloid* or sodium chloride* or ringer lactate* or colloid* or hydroxyethyl starch*).mp.

16 (vasopressor* or catecholamine* or vasoconstrictor* or norepinephrin* or dobutamin* or dopamin* or epinephrin* or vasopressin* or angiotensin II or ornipressin* or felypressin* or arginine asopressin* or orciprenaline* or phenylephrine* or levosimendan* or metaraminol* or milrinone* or amrinone* or albumin* or dextran* or starch* or glucocortico* or hydrocortison* or fludrocortison* or gelatin*).mp.

17 (((blood or plasma) adj2 (product* or frozen or freez* or fresh)) or ((rais* or ris* or increas*) adj3 blood pressur*)).mp.

18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 exp Shock/

20 shock*.mp.

21 19 or 20

22 18 and 21

23 ((randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or clinical trials as topic.sh. or random allocation.sh. or trial.ti.) not (exp animals/ not humans.sh.)

24 22 and 23

25 (exp child/ or child*.mp. or p?ediat*.mp. or neonat*.mp. or newborn*.mp. or infant*.mp. or adolesc*.mp. or teen*.mp.) not (exp adult/ or adult*.mp. or aged.mp. or elderly.mp. or middle age.mp.)

26 24 not 25

Appendix 2. 'Risk of bias' assessment

Allocation sequence generation

1. Low risk: if sequence generation was achieved using computer random number generator or a random numbers table. We will consider drawing lots, tossing a coin, shuffling cards, and throwing dice as adequate if performed by an independent adjudicator.
2. Unclear risk: if the method of randomization was not specified, but the trial was still presented as being randomized.
3. High risk: if the allocation sequence was not randomized or only quasi-randomized.

Allocation concealment

1. Low risk: if the allocation of patients was performed by a central independent unit, on-site locked computer, using identical-looking numbered sealed envelopes, drug bottles, or containers prepared by an independent pharmacist or investigator.
2. Uncertain risk: if the trial was classified as randomized but the allocation concealment process was not described.
3. High risk: if the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

1. Low risk: if the participants and the treatment providers (except the one prescribing the interventions to adjust the blood pressure) were blinded to intervention allocation and this was described.
2. Uncertain risk: if the procedure of blinding was insufficiently described.
3. High risk: if blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

1. Low risk of bias: if it was mentioned that outcome assessors were blinded and this was described.
2. Uncertain risk of bias: if it was not mentioned if the outcome assessors in the trial were blinded, or the extent of blinding was insufficiently described.
3. High risk of bias: if no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

1. Low risk of bias: if missing data were unlikely to make treatment effects depart from plausible values. This could either be:
   a. there were no drop-outs or withdrawals for all outcomes, or
   b. the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar in both groups. Generally, the trial was judged to be at a low risk of bias due to incomplete outcome data if drop-outs were less than 5%. However, the 5% cut-off was not definitive.
2. Uncertain risk of bias: if there was insufficient information to assess whether missing data were likely to induce bias on the results.
3. High risk of bias: if the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

1. Low risk of bias: if a protocol was published before or at the time the trial was begun and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial has begun, reporting of all-cause mortality and serious adverse events will grant the trial a grade of low risk of bias.
2. Uncertain risk of bias: if no protocol was published and the outcomes all-cause mortality and serious adverse events were not reported on.
3. High risk of bias: if the outcomes in the protocol were not reported on.

Other bias

1. Low risk of bias: if the trial appears to be free of other components (for example, academic bias or for-profit bias) that could put it at risk of bias.
2. Unclear risk of bias: if the trial may or may not be free of other components that could put it at risk of bias.
3. High risk of bias: if there are other factors in the trial that could put it at risk of bias (for example, authors have conducted trials on the same topic, for-profit bias etc) .

Overall risk of bias

We will assess overall risk of bias in two groups defined as:

1. Low risk of bias: we will classify the outcome result as overall at 'low risk of bias' only if we classify all of the bias domains described in the above paragraphs as low risk of bias.
2. High risk of bias: we will classify the outcome result as 'high risk of bias' if we classify any of the bias risk domains described in the above as 'unclear' or 'high risk of bias'.

We will assess the domains 'Blinding of outcome assessment', 'Incomplete outcome data', and 'Selective outcome reporting' for each outcome. Thus, we will be able to assess the bias risk for each result in addition to each trial. We will base our primary conclusions as well as our presentation in the 'Summary of findings' table on the results of our primary outcomes with low risk of bias.

We will grade each potential source of bias as high, low, or unclear and provide a quote from the trial report together with a justification for our judgement in the 'Risk of bias' table. We will summarize the 'Risk of bias' judgements across different trials for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trial author, we will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the trials that contribute to that outcome.

Appendix 3. Trial sequential analysis (TSA)

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (Brok 2008; Brok 2009; Higgins 2011b; Pogue 1997; Thorlund 2009; Wetterslev 2008; Wetterslev 2017). Trial sequential analysis (TSA), CTU 2011, can be applied to control these random errors and to assess the risks of imprecision (www.ctu.dk/tsa/) (Castellini 2018; Gartlehner 2019; Jakobsen 2014; Thorlund 2011). The required information size calculated by TSA takes into account the event proportion in the control group, the assumption of a plausible RR reduction, and the heterogeneity of the meta-analysis (Turner 2013; Wetterslev 2009).

For dichotomous outcomes, previous data suggests the effect size to be a relative RR of 8.3% (Lamontagne 2018). However, we will estimate the required information size based on the proportion of patients with an outcome in the control group and a relative RR of 7.5% (a bit more conservative than the existing data), an alpha of 3.3%, a beta of 20%, and a variance suggested by the trials in a random-effects meta-analysis (diversity-adjusted required information size) (Jakobsen 2014; Wetterslev 2009). In case there is some evidence of effect of the intervention, a supplementary TSA will use the limit of the confidence interval closest to 1.00 as the anticipated intervention effect (Jakobsen 2014). Additionally, we will calculate the TSA-adjusted confidence interval (CI).

For continuous outcomes, we have not identified valid previous data on effect sizes on quality of life so we have chosen to use standard deviation (SD)/2 as anticipated intervention effect. Hence, we will estimate the required information size based on the SD observed in the control group of trials with low risk of bias or lower risk of bias and a minimal relevant difference of the observed SD/2 , an alpha of 3.3%, a beta of 20%, and a diversity suggested by the trials in the meta-analysis (Jakobsen 2014; Wetterslev 2009). In case there is some evidence of effect of the intervention, as a supplementary TSA we will use the limit of the CI closest to 0.00 as the anticipated intervention effect (Jakobsen 2014). Additionally, we will calculate TSA-adjusted CI.

CONTRIBUTIONS OF AUTHORS

Steven Kwasi Korang (SKK), Sanam Safi (SS), Joshua Feinberg (JF), Christian Gluud (CG), Anders Perner (AP), Janus C Jakobsen (JCJ).

SKK conceived and coordinated the protocol, and is the guarantor of the protocol.

All protocol authors read and approved the final protocol.

DECLARATIONS OF INTEREST

Steven Kwasi Korang: no conflict of interest.

Sanam Safi: no conflict of interest.

Joshua Feinberg: no conflict of interest.

Christian Gluud: no conflict of interest.

Anders Perner: the Department of Intensive Care, where AP heads the research unit, receives support for research from CSL Behring, Fresenius Kabi, and Ferring Pharmaceuticals.

Janus C Jakobsen: no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Denmark.

External sources

- No sources of support supplied